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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,954	05/24/2002	Eric Samain	065691-0267	6242

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,954	SAMAIN ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-24 and 26-46* is/are pending in the application.

4a) Of the above claim(s) *15-17,21-24,29,31-38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-14, 18-20, 26-28, 30, and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 3, 4, and 25 have been canceled. Claims 1, 2, 5-24 and 26-46 are still at issue and are present for examination.

Applicants' arguments filed on 5/30/06, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 15-17, 21-24, 29, 31-38, and 40-46 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/13/05.

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. As amended Claim 14 does not further limit Claim 1 as all of the precursors of Claim 1 (i.e., lactose, sialic acid, α-galactosides, and β-galactosides) are carbohydrates.

Claims 1, 2, 5-14, 18-20, 26-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants response merely reiterates their previous argument that the specification provides lists of suitable genes, precursors, and types of cells, and specific examples of suitable genes, precursors, and types of cells and thus that the description of genes, precursors, and types of cells that can be used to practice the claimed invention is adequate in light of the knowledge of one of skill in the art and notes that the claims have been amended to limit the cells to bacterial cells and lactose, sialic acid, α-galactosides, or β-galactosides as exogenous precursor. As was previously stated, merely providing lists of sources of each individual component is insufficient to provide an adequate written description of the methods recited in the claims as each gene cannot be used with each with every precursor in every microorganism for the synthesis of any desired oligosaccharides. Practicing the methods of the claims requires detailed knowledge of the biosynthetic pathways for the synthesis of any desired oligosaccharide, knowledge of the source of all enzymes necessary for such synthesis, knowledge of

the metabolic/catabolic pathways present in the microorganism to be used and detailed knowledge of how these factors are interrelated such that one obtains the desired result. Oligosaccharides encompass an enormous family of highly complex compounds which are synthesized by highly complex biosynthetic pathways by an enormous number of different enzymes many of which are present in only a small number of microorganisms. Wild type *E. coli* produce only a very limited number of oligosaccharides while other microorganisms may produce different oligosaccharides by pathways that are only poorly defined in the art. Furthermore, while genes for the synthesis of some specific oligosaccharides are provided by the specification and/or prior art, use of any combination thereof for the production of any oligosaccharide is not a straightforward process involving only the transformation of a single gene into *E. coli* and expression of this gene therein. For many oligosaccharides to be produced multiple genes are necessary only some of which may be available in the prior art, the biosynthetic pathways as well as competing metabolic processes are not well defined, and all necessary precursors may not be present or may not be present in sufficient amounts. As such the specifications provision of a laundry list of known genes, precursors, and types of cells is insufficient to

describe the breadth of the claimed methods. Furthermore, applicants amendments to limit the claims to using bacterial cells and lactose, sialic acid, an α-galactoside, or a β-galactoside as exogenous precursor do not limit the claims to that which is sufficiently described. The limitation of the cells to bacterial cells is insufficient as bacteria are enormously diverse such that the introduction of this limitation does little limit the scope of knowledge necessary to produce any oligosaccharide within any bacteria. Furthermore, while applicants have limited the claims to using lactose, sialic acid, an α-galactoside, or a β-galactoside as the exogenous precursor, these compounds are precursors for an enormous number of different oligosaccharides each of which would require different enzymes and would interact differently with the endogenous pathways of the bacterial host. As such the rejection is maintained.

Claims 1-14, 18-20, 25-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making lacto-N-neotetraose or polylactosamine from lactose using Lac Z^- *E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes, does not reasonably provide enablement for methods of making any oligosaccharide from lactose, sialic acid, an α-galactoside, or

a β-galactoside in any bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants appear to believe that the amendments to the claims to limit the claims to using bacterial cells and lactose, sialic acid, an α-galactoside, or a β-galactoside as exogenous precursor is sufficient to overcome the instant rejection.

However, these limitations are not sufficient as the genus of bacteria is enormous as is the genus of oligosaccharides which can be produced from lactose, sialic acid, an α-galactoside, or a β-galactoside. As such a skilled artisan would still require detailed knowledge of the biosynthetic pathways for the synthesis of any oligosaccharides which can be produced from lactose, sialic acid, an α-galactoside, or a β-galactoside (which is an essentially infinite genus of possible compounds), knowledge of the source of all enzymes necessary for such synthesis, knowledge of the metabolic/catabolic pathways present in the bacteria to be used and detailed knowledge of how these factors are interrelated such that one obtains the desired result. It is well known in the art that oligosaccharides are a highly diverse group of compounds that encompass an enormous

diversity of monosaccharide units which can be linked to one another in a vast array of distinct types of linkages. It is further known in the art that each distinct linkage is generally catalyzed by a distinct enzyme (i.e., glycosyltransferase) and that glycosyltransferases that catalyze different linkages generally have little of no structural homology to each other. The claims recite methods of making any oligosaccharide in any bacterium, requiring the use of an enormous number of different glycosyltransferase genes. The specification teaches only a few such genes which clearly do not provide a skilled artisan the ability to catalyze the synthesis of any possible oligosaccharide linkage desired. Furthermore, the vast majority of known glycosyltransferase genes are eukaryotic in origin and seldom can be expressed easily in bacteria, even further limiting the scope of available glycosyltransferase genes which could be used in the claimed methods. Furthermore, the claimed methods recite the use of any bacterium, including the use of bacteria modified in a variety of ways to prevent the degradation of the oligosaccharide of interest. The specification clearly does not teach sufficient guidance for the use of any such bacteria as bacteria are highly diverse in their abilities to degrade carbohydrates as well as the pathways used to do so. As such, the modification of one bacteria such that

it does not degrade a oligosaccharide of interest cannot be considered to provide guidance for the use of other bacteria as the types of modifications which would be necessary for even that same oligosaccharide to be produced by any bacteria would clearly be different in other bacteria and clearly would not would not provide guidance for the types of modifications necessary for the production of other oligosaccharides. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5-14, 18-20, 26-28, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettler et al. in view of Kozumi et al. The rejection was explained in the previous Office Action as applied to claims 18-20, 27, 28, and 39 and is now applied to all of claims 1, 2, 5-14, 18-20, 26-28, and 39 in view of the amendments to claim 1 to limit the scope of exogenous precursors.

Applicants argue that one of skill in the art would have no motivation to combine Bettler and Kozumi, much less any expectation of success as it was known in the art that rapid uptake of sugars by lactose permease disrupts membrane function, possibly by causing collapse of the membrane potential and results in growth inhibition and eventually cell death (i.e., lactose killing). See Wilson et al., Biochim. Biophys. Acta 649(2):377-84 (1981, Exhibit A); Dykhuizen et al., J. Bacteriology 135(3):876-82 (1978, Exhibit B); and Ahmed et al., J. Gen. Microbiol. 129(8):2521-29 (1983). Given this knowledge in the art, a skilled artisan would have no reason to combine the teachings of Bettler and Kozumi, much less have an expectation of success. However, this is not persuasive because lactose killing as reported in the cited references is present in *E coli* cells that have been growing on a limited supply of lactose when they are then provided with excess lactose but not

in cells growing on other carbon sources when supplied with lactose (see Dykhuizen et al.) however, the rejection does not suggest this at all. Instead it suggests growth of cells on glycerol (Bettler et al.) or glucose (Kozumi et al.). Furthermore, as reported in Ahmed et al. the amount of growth inhibition produced by lactose can be diminished by growing the cells in buffers with a pH of about 6.0, high levels of Na^+ and low levels of K^+ and/or by reducing the rate of import of lactose into the cell (see Ahmed et al. and Dykhuizen et al.) and a skilled artisan would be aware that even a low growth rate of the cells could still be sufficient to produce large amounts of the desired product. In fact artisans would clearly be aware that many products of interest produced in bacteria are produced only at the end stage of a fermentation when the cells are only growing slowly or have stopped growing and skilled artisans are clearly provided with the tools (i.e., inducible promoters) to control the rate of production of the lactose permease such that the rate of influx of lactose could adjusted so as to limit lactose influx mediated growth inhibition. As such a skilled artisan would not have lacked motivation of expectation of success in view of the disclosures cited by applicants.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bettler et al. in view of Kozumi et al. as

applied to claims 1, 2, 5-14, 18-20, 26-28, and 39 above, and further in view of Johnson and Gotschlich (WO 96/10086). The rejection is explained in the previous Office Action.

Applicant has not presented any arguments specifically traversing this rejection but instead relies upon the traversal discussed above. Therefore, this rejection is maintained for the reasons presented above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652